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Association between Vitamin D and Allergy-Related Outcomes Vary by Race and other Factors

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Abstract

Background—Allergy-related studies that include biological measurements of vitamin D preceding well-measured outcomes are needed.

Objective—Examine the associations between early life vitamin D levels and the development of allergy-related outcomes in the racially diverse WHEALS birth cohort.

Methods—25-hydroxyvitamin D [25(OH)D] was measured in stored blood samples from pregnancy, cord blood and age 2 years. Logistic regression models were used to calculate odds ratios (OR) with 95% confidence intervals (CI) for a 5 ng/ml increase in 25(OH)D level for the outcomes at age 2 years: eczema, skin prick tests (SPT), elevated allergen-specific IgE (sIgE≥0.35IU/ml), and doctor diagnosis of asthma (3–6 years).

Results—Prenatal 25(OH)D was inversely associated with eczema (OR=0.85, 95% CI 0.75, 0.96). The association was stronger in White children (White: OR=0.79, 95% CI 0.57, 1.09; Black: OR=0.96, 95% CI 0.82, 1.12), although this was not statistically significant. Cord blood 25(OH)D was inversely associated with having ≥1 positive SPT and aeroallergen sensitization. Both associations were statistically significant in White children (SPT: OR=0.50, 95% CI 0.32, 0.80; ≥1 aeroallergen: OR=0.50, 95% CI 0.28, 0.92) in contrast with Black children (SPT:OR=0.88, 95% CI 0.68, 1.14; aeroallergen: OR=0.85, 95% CI 0.65, 1.11). 25(OH)D measured concurrent with outcome assessment was inversely associated with aeroallergen sensitization (OR=0.79, 95% CI 0.66, 0.96) only among Black children (White children: OR=1.21, 95% CI 0.87, 1.69).

Conclusions—Prenatal and cord 25(OH)D were associated with some allergy-related outcomes with a general pattern indicating that children with higher 25(OH)D tend to have fewer allergy-related outcomes.

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Keywords

vitamin D; allergy; eczema; asthma; IgE; racial differences

INTRODUCTION

Interest in vitamin D's role in allergic disease incidence has grown tremendously in recent years, particularly since vitamin D supplementation is perceived as affordable, non-invasive and easily administered. Overall, the evidence regarding whether vitamin D affects the incidence of allergy-related outcomes is mixed due to reliance of many studies on the use of parental- or self-reported outcomes and food frequency questionnaires (FFQ). [1–3] FFQs approximate dietary vitamin D intake rather than reflect bioavailable levels, which are also influenced by sun exposure and supplement intake. The number of studies that include a direct measurement of vitamin D (25-hydroxyvitamin D [25(OH)D] or $25(OH)D_2$ or $25(OH)D_3$) that clearly preceded childhood allergic disease incidence are growing in number. [4–8] Other studies continue to measure vitamin D concurrent with the clinical outcomes.[9–12]

The mechanism by which vitamin D may alter immune development and immune related diseases has been proposed to be one in which vitamin D directly and indirectly affects the immune system.[13] In their review of the influences of gut microbiota, probiotics and vitamin D on allergies and asthma, Ly et al. suggested that vitamin D may be an important modifier of the association between intestinal flora and inflammatory disorders.[14] Recent discussion that low levels of vitamin D may be a risk factor for developing inflammatory bowel diseases such as Crohn's disease suggest that vitamin D can affect gut inflammation.[15–17] This gut inflammation could, in turn, affect immune development and function which can subsequently manifest itself in the first readily observable inflammatory diseases – eczema and allergies.[18]

There were multiple objectives for this work. The first goal was to examine whether serum levels of 25(OH)D collected at various time points (during pregnancy, delivery and at the time of a clinical evaluation at approximately age 2 years) were related to the incidence of eczema, elevated allergen-specific IgE (sIgE) and skin prick testing (SPT) in the first two years of life or related to parental report of doctor diagnosis of asthma at age 3–6 years. We also sought to assess whether any associations differed between Black children and White children. Finally, we compared associations between 25(OH)D and the outcomes at different timepoints of 25(OH)D measurement in order to examine whether the associations varied with timing of sample collection (i.e., prenatal sample versus cord sample). We thought this sample timing variation could be contributing to the conflicting evidence in the literature investigating the role of vitamin D in allergic disease development.

METHODS

Study Population

"WHEALS" is an NIH and institutionally funded cohort study that enrolled pregnant women receiving care at Henry Ford Health System (HFHS) obstetrics clinics in the Detroit, Michigan, USA area for longitudinal study of their children through early childhood with the goal of examining early life exposures related to childhood allergies and asthma. These children and their mothers served as the source population for the analyses. Details of cohort creation have been published.[19–21] The children included in this study have information on at least one outcome at age 2 years (results from SPT, total IgE, sIgE, or physician evaluation of eczema) or participated in a health interview when the child was 3–6 years of age (mean age=4.2 years, SD=0.9). We are also including only those children who are African American and White/Non-Hispanic/Non-Middle Eastern to best examine racial differences. The subgroups of children who are White/Hispanic or White/Middle Eastern are too few in number to analyze as subgroups in this study.

Figure 1 provides details describing the inclusion and exclusion of participants. Some children completed the 2 year clinic visit, but did not complete all aspects of the clinical protocol. For example, they may have had skin prick testing but did not have a blood sample with sufficient volume to permit analyses of sIgEs. If a child had a result for an outcome, they were included in the analyses.

Interviews

Parents were interviewed about the health of their children (allergic diseases, symptoms/diagnoses), breastfeeding, and exposure to animals at 1, 6 and 12 month home visits and at 2 years of age (included data since the last contact). Health updates were obtained with parental interview at child age 3–6 years during which the parents were asked to report whether the child had ever received a diagnosis of asthma from a doctor.

Allergic Diseases

All children were invited for a standardized exam with skin prick testing and parental interview at age 2 years with a physician trained in the study protocol. The physicians discussed allergy symptoms and examined the child for any eczema. Skin prick testing for *Dermatophagoides farinae*, dog, cat, timothy grass, ragweed, *Alternaria alternata*, egg, peanut, milk, and German cockroach was performed. A positive skin test was defined as one producing a wheal with the longest diameter ≥3 mm greater than the negative control. Allergen-specific IgEs were also measured for the same allergens among those who provided a blood sample at age 2 years. sIgE levels in mothers' prenatal blood samples were assessed for a subset of the allergens (*Dermatophagoides farinae*, dog, cat, timothy grass, ragweed, *Alternaria alternata*, egg and German cockroach) using the same methods. Atopy was defined as having at least one sIgE ≥0.35 IU/ml.

Vitamin D

25(OH)D, representing the sum of $25(OH)D_2$ (ergocalciferol which is diet related) and $25(OH)D_3$ (cholecalciferol which is sun related), was measured in frozen plasma samples

(−80°C) in the laboratory of Dr. Neil Binkl ey at the University of Wisconsin. An HPLC method was used and has been used in previously published research.[22–28] 25(OH) is expressed in ng/ml. 25(OH)D was measured in the stored samples from pregnancy, delivery (cord blood) and at age 2 years. Vitamin D levels can be affected by the time of year (seasonal effects) and adjustment for this variation is possible. The seasonal variation of serum 25(OH)D was modeled with a sinusoidal model of the values (25(OH)D value) and time (month denoted as m) of collection:

$$25(\mathrm{OH})\mathrm{D\ level}=\beta_0+\beta_1\sin(2\pi\mathrm{m}/12)+\beta_2\cos(2\pi\mathrm{m}/12)$$

Seasonally adjusted values (called deseasonalized by van der Mei et al.) were then calculated by taking each subject's value and subtracting the predicted value and adding back in the overall mean.[29] The seasonally adjusted 25(OH)D levels were used in the analyses detailed below.

Statistical Analyses

Logistic regression models were calculated for a 5 ng/ml increase in 25(OH)D level for each analytical outcome (eczema, SPT, atopy, food atopy, inhalant allergen (aeroallergen) atopy, doctor diagnosis of asthma) for all children and separately for Black and White children. Means and standard deviations of the deseasonalized 25(OH)D levels were calculated and compared across groups using t-tests at the various collection timepoints. This was done for all children and separately for Black and White children. Additional logistic regression models were run to investigate potential heterogeneity of associations (i.e., effect measure modification)[30] between 25(OH)D and each allergic disease outcome by the following variables: maternal atopic status (yes/no), maternal prenatal use of antibiotics or vaginally applied antifungal medications (yes/no), mother lived with a dog during pregnancy (yes/no), child lived with a dog in the first year of life (yes/no), delivery mode (vaginal or not), firstborn status (yes/no), breast fed (yes/no), baby gender, home ownership (yes/no), maternal education (less than high school diploma/at least a high school diploma) and household income (<$40,000/≥$40,000). While sample size limited the precision of these estimates in these subgroups, we thought it important to consider possible effect modification as there is a paucity of evidence on the associations between vitamin D and allergy-related outcomes in subgroups. A likelihood ratio test was performed to compare 25(OH)D quintiles to the linear model to assess possible non-linearity. Finally, we reran our analyses including samples only from maternal/child pairs who contributed samples from both pregnancy and cord blood to evaluate whether the results for each time-point were similar.

Because our goal was to examine relationships between 25(OH)D levels and allergy-related outcomes, potential confounders were considered in evaluating these associations. The same factors that were examined for potential effect modification were assessed as potential confounders. We examined whether any of these factors were associated with any of the 25(OH)D measures and any of the outcomes. Only living with a dog during pregnancy and living with a dog in the 1st year were associated with both. When we adjusted the models for these factors, the associations were unchanged.

RESULTS

Characteristics of children included and not included in the analyses are presented in Table 1. The groups were quite similar with respect to rates of maternal sensitization, delivery type, race and firstborn status. Those included in the analyses were more likely to have had a mother who resided with an indoor dog during pregnancy.

Table 2 presents the means (standard deviations) of the deseasonalized 25(OH)D levels for all children included in the analyses, and separately for Black children and White children. White children tended to have higher levels of 25(OH) at each time point (prenatal, cord blood, 2 years) compared to the means of the Black children. The rates of each outcome overall and separately for White children and Black children are presented in Table 3. Our previous publication demonstrated the Black children have higher rates of each outcome in this birth cohort.[19] More than half of the Black children and more than a third of the White children were atopic. More than a quarter of the Black children had a history of eczema – more than double the rate of the White children. While only 9.9% of the White children had received a doctor diagnosis of asthma, 14.7% of the Black children had.

The associations between vitamin D and each allergy-related outcome were then examined using odd ratios (OR) and 95% confidence intervals (CI) for a 5 ng/ml increase in 25(OH)D. The associations are presented by each time-point for all children and separately for White children and Black children (Table 4). An increase in the prenatal level of 25(OH)D was associated with decreased odds of eczema (OR=0.85, 95% CI 0.75, 0.96), overall, and the association was stronger, although not statistically significantly, in the White children (OR=0.79, 95% CI 0.57, 1.09) compared with the Black children (OR=0.96, 95% CI 0.82, 1.12). Higher levels of cord blood 25(OH)D were also associated with decreased odds of having at least one positive skin prick test (OR=0.77, 95% CI 0.62, 0.94) and being sensitized to at least one aeroallergen (OR=0.74, 95% CI 0.58, 0.94). Both associations were statistically significant in the White children (SPT: OR=0.50, 95% CI 0.32, 0.80; ≥1 aeroallergen: OR=0.50, 95% CI 0.28, 0.92) but not the Black children (SPT: OR=0.88, 95% CI 0.68, 1.14; aeroallergen: OR=0.85, 95% CI 0.65, 1.11). Among Black children only, higher 25(OH)D at the time of the clinic visit was associated with decreased odds of being sensitized to at least one aeroallergen (OR=0.79, 95% CI 0.66, 0.96). This was not true for the White children (OR=1.21, 95% CI 0.87, 1.69). These results are similarly reflected by statistically significant differences in mean levels of 25(OH)D (Online Table 1).

Stratum-specific estimates were examined for any interaction term where $p \leq 0.05$ to investigate possible heterogeneity of associations. Higher prenatal 25(OH)D was associated with decreased odds of having any sensitization among children born to atopic mothers (atopic mother: OR=0.89, 95%CI 0.78, 1.02; mother not atopic: OR=1.10, 95%CI 0.95, 1.27) (Table 5). Prenatal 25(OH)D varied in its association with doctor diagnosis of asthma at age 3–6 years based on delivery mode: c-section, OR=1.16, 95%CI 0.91, 1.48; and vaginal delivery, OR=0.86, 95% CI 0.75, 0.98 (Table 5). Associations between prenatal 25(OH)D and eczema varied by maternal education (less than high school: OR=0.76, 95% CI 0.64, 0.90; at least high school: OR=1.06, 95% CI 0.86, 1.30) and the associations between prenatal 25(OH)D and having at least one elevated inhalant sIgE also varied by

household income (≥$40,000: OR=0.77, 95% CI 0.60, 0.97; <$40,000: OR=1.03, 95% CI 0.88, 1.20).

We reran the models using different approaches. First, we included season as a covariate with the deseasonalized variable and all results were unchanged. The results were also unchanged when the models were rerun using the actual 25(OH)D values and a covariate to adjust for season. No nonlinear associations were found using Likelihood Ratio Tests (all $p>0.05$).

Finally, a limited set of analyses were run on the subset of children who had both a prenatal and cord blood sample (n=304). The 25(OH)D levels in the prenatal and cord samples were more strongly correlated (Spearman r=0.74) compared with the associations between the prenatal levels and the cord levels with the levels at age 2 years (r=0.34 and r=0.33, respectively). Mean levels for each time-point are presented separately for Black and White children in Online Table 2. As expected, Black children tended to have lower levels than White children. Prenatal 25(OH)D was not statistically significantly associated with any of the outcomes; however, cord blood 25(OH)D level was inversely associated with being sensitized overall (OR=0.81, 95% CI 0.66, 0.99) and being sensitized to an aeroallergen (OR=0.71, 95% CI 0.53, 0.96). This was true when either the OR for a 5 unit change in 25(OH)D or the differences in means of those who were and were not sensitized were compared (Online Tables 3 and 4).

DISCUSSION

In this cohort study, 25(OH)D was associated with some allergy-related outcomes. The general pattern of the results indicates that children with higher 25(OH)D tended to have fewer allergy-related outcomes. More specifically, higher prenatal 25(OH)D was associated with lower odds of eczema, with stronger, albeit not statistically significantly different, associations in the White children compared to the Black children. Cord blood 25(OH)D was inversely associated with the odds of having at least one positive skin prick test and being sensitized to at least one aeroallergen. Both associations were statistically significant only in the White children. However, among only Black children, higher 25(OH)D at the time of the clinic visit was associated with decreased odds of being sensitized to at least one aeroallergen. Prenatal 25(OH)D was positively associated with the odds of a doctor diagnosis of asthma among children born via c-section, but inversely associated in children born vaginally. Additional subgroup analyses suggest that maternal atopic status may modify the associations between prenatal 25(OH)D and developing atopy. Furthermore, prenatal 25(OH)D was inversely associated with eczema in children with mothers who had less education and inversely associated with being sensitized to aeroallergens among children from families with higher income. The data suggest that maternal atopic status, education and household income and delivery mode may need to be incorporated into any vitamin D study's design, and sample size, recruitment and analytical plans.

In children with both a prenatal and cord blood 25(OH)D sample, some of the associations between vitamin D and the outcomes differed by whether the sample was collected prenatally or at delivery (cord blood). Differences existed in both the estimates of the ORs

and the statistical significance. These discrepancies have potential implications for both study design and interpretation of the literature. While not conclusive, these data support the need for further investigation.

While vitamin D has been considered a treatment for atopic dermatitis (AD),[31] there have been few investigations of the relationship between early life vitamin D levels and childhood AD risk. Children whose mothers had the highest quartiles of 25(OH)D during pregnancy had an increased risk of AD at age 9 months in a birth cohort of 440 English infants (OR=3.26, 95%CI 1.15, 9.29).[32] In the ALSPAC birth cohort, prenatal 25(OH)D levels were not associated with eczema assessed by questionnaire among 7–8 year old children.[7] In an Australian cohort (n=231) in which the children had at least 1 allergic parent, cord blood 25(OH)D_3 was weakly inversely associated with eczema (as defined by clinical examination or parental report of doctor diagnosis) at 1 year of age (OR=2.66, 95% CI 1.24,5.72 for 25(OH)D_3 <50 nmol/l versus ≥75 nmol/l).[8] Cord blood 25(OH)D levels were also inversely associated with AD (assessed by questionnaire) by age 5 years in children (n=239) in the EDEN birth cohort (adjusted OR=0.75, 95% CI 0.63, 0.88).[6] These inconsistent results could be due to the use of outcomes defined by questionnaire data rather than a clinical examination and that prenatal and cord blood may not be considered as interchangeable measures of early life vitamin D as suggested in the current analyses.

While higher cord 25(OH)D levels were associated with decreased odds of having a positive skin prick test in our study population, prenatal 25(OH)D levels were not associated with childhood skin prick test results in either the ALSPAC cohort [7] or the Southampton Women's Survey (n=860)[33] nor were associations found between cord blood 25(OH)D_3 and skin prick tests in the Perth cohort [8]. Higher prenatal and cord blood 25(OH)D_3 were associated with increased risk of food allergy (report of doctor diagnosis) at age 2 years in the German LINA cohort (n=272) (adjusted OR=4.65, 95% CI 1.50, 14.48)[34] and high cord blood 25(OH)D levels were associated with increased rates of having a positive skin prick test (OR=4.2, 95% CI 1.2, 2.7) while both high and low 25(OH)D levels were associated with higher levels of total IgE in the Tucson Infant Immune Study.[35]

The study in Southampton, UK, although limited by loss to follow-up (30% remained at age 9 years), found that higher 25(OH)D levels in late pregnancy were associated with increased frequency of asthma at age 9 based on maternal report (OR=5.40, 95% CI 1.09, 26.65).[32] Prenatal 25(OH)D level was not associated with lung function in the ALSPAC cohort[7] or with childhood asthma in the Southampton Women's Study[33] and cord blood 25(OH)D was not associated with asthma at age 5 years as defined by parental report in the EDEN study[6] or New Zealand Allergy and Asthma cohort (n=922; parental report of doctor diagnosis of asthma).[36]

While the results of the present study do not suggest that vitamin D, represented by circulating 25(OH)D, is overwhelmingly associated with disease causation, the data do suggest that vitamin D may play a role with importance that varies depending on other risk factors present in an individual. Prescott cites speculation that vitamin D may actually be a proxy for UV exposure that can affect reduction in an individual's propensity for

inflammation[18]. If this is the case, then it would be important to note that vitamin D supplementation would not overcome the effects of a UV deficiency.[18]

There are numerous strengths to this work. We investigated multiple time points for their association with outcomes that were established at a clinic visit and with report of doctor diagnoses rather than through the use of interview data to assess clinical and other allergy-related outcomes. Two of the time points analyzed clearly precede “disease” incidence. The analyses also include Black and White children from the same region who were not recruited based on allergic disease status or family history. Finally, the subgroup analyses add important information suggesting that the role of vitamin D may vary within subgroups.

Unfortunately, we do not have more frequent measures of 25(OH)D, which is a limitation. Additionally, the parental report of a doctor diagnosis of asthma may lack sensitivity as diagnosing asthma in young children is challenging; however, recent reports suggest the strong possibility of high specificity of this methods. Yang et al. recently reported that when compared to an asthma diagnosis based on claims data, parental report of a doctor diagnosis of asthma was not sensitive (59%) but was specific (95.9%).[37] A larger sample size would have improved the precision of the associations in the subgroups. Some of our associations could be spurious findings.

As previously suggested, direct measurement of vitamin D and specific measurement of the outcomes are critical to improving our understanding of any potential role that vitamin D might play in developing allergy-related health conditions.[13] We further add that consideration of the possibility that the role vitamin D may play in causation is one of relative importance that may depend on other factors present. Observational studies and clinical trials will only be able to uncover this role if the studies are adequately designed and powered to conduct the important subgroup investigations.

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Abbreviations

sIgE	allergen-specific IgE
SPT	Skin Prick Test

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Clinical Implications (2–3 bullet points)

- Prenatal 25(OH)D was inversely associated with eczema and cord blood 25(OH)D was inversely associated with SPT and aeroallergen sensitization. Strengths of the associations varied between Black children and White children.
- The associations between vitamin D and some allergy-related outcomes may vary within subgroups and observational studies and clinical trials should account for these subgroups in the design and analyses.

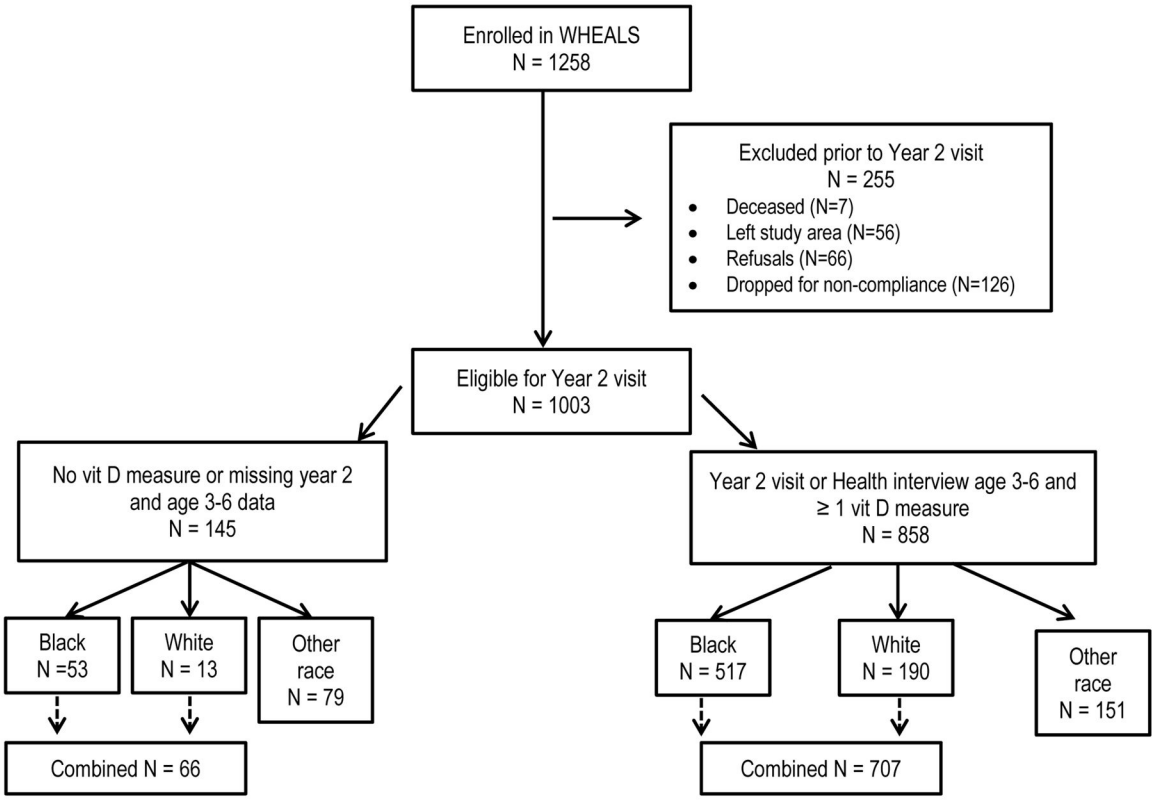

Figure 1.

Details of the inclusion and exclusion of WHEALS study participants in the current analyses.

Table 1

Comparison of women from WHEALS whose children were included and excluded from the current analyses.*

	Women with a Child Included in the Analyses	Women with a Child Excluded from the Analyses	p value
N	707	66	
Ever breastfed the child (n(%) yes)	522 (77.4%)	41 (69.5%)	0.17
Mother had an indoor dog during pregnancy	201 (28.4%)	10 (15.2%)	0.021
Child lived with an indoor dog in the first year of life	183 (27.3%)	10 (16.7%)	0.074
Mother sensitized to allergens	400 (58.1%)	34 (56.7%)	0.82
Child's gender			
Male	357 (50.5%)	34 (51.5%)	0.87
Female	350 (49.5%)	32 (48.5%)	
Race			
Black	517 (73.1%)	53 (80.3%)	0.21
White	190 (26.9%)	13 (19.7%)	
Delivery type			
Vaginal	451 (63.9%)	36 (54.6%)	0.13
C-section	255 (36.1%)	30 (45.4%)	
Child was firstborn	273 (38.6%)	21 (31.8%)	0.28

*There are some missing data. P-values are for a comparison of those included and those excluded.

Table 2

Mean (SD) for 25(OH)D at each time point (in ng/ml).*

25(OH)D	Black children	White children	All children	P value for Black versus White children*
Prenatal	19.5 (9.5) N=380	33.1 (11.2) N=144	23.2 (11.7) N=524	<0.001
Cord	8.9 (6.3) N=315	16.7 (7.6) N=101	10.8 (7.4) N=416	<0.001
2 Years	23.0 (7.8) N=283	26.3 (8.4) N=96	23.8 (8.1) N=379	<0.001

* p-value for t-test; 25(OH)D levels have been deseasonalized

Table 3

Rates of each outcome for those included in the current analyses.

25(OH)D	Eczema ever	SPT+	≥1 sIgE ≥ 0.35 IU/ml	≥1 food allergen sIgE ≥ 0.35 IU/ml	≥1 aeroallergen sIgE ≥ 0.35 IU/ml	Doctor diagnosis of asthma at 3–6 years
All Children	116/516 (22.5%)	123/506 (24.3%)	226/454 (49.8%)	188/468 (40.2%)	106/450 (23.6%)	85/635 (13.4%)
White Children	18/153 (11.8%)	25/148 (16.9%)	46/117 (39.3%)	36/125 (28.8%)	19/115 (16.5%)	17/172 (9.9%)
Black Children	98/363 (27.0%)	98/358 (27.4%)	180/337 (53.4%)	152/343 (44.3%)	87/335 (26.0%)	68/463 (14.7%)

Table 4

Odds ratios (95% CI) associated with 5 ng/ml change in 25(OH)D.

25(OH)D	Eczema ever	SPT+	≥1 sIgE ≥ 0.35 IU/ml	≥1 food allergen sIgE ≥ 0.35 IU/ml	≥1 aeroallergen sIgE ≥ 0.35 IU/ml	Doctor diagnosis of asthma at 3–6 years
Prenatal	**0.85 (0.75–0.96)**	0.95 (0.85–1.06)	0.97 (0.85–1.07)	0.97 (0.88–1.07)	0.91 (0.81–1.03)	0.92 (0.82, 1.03)
Cord	0.88 (0.72–1.08)	**0.77 (0.62–0.94)**	0.86 (0.73–1.02)	0.91 (0.77–1.07)	**0.74 (0.58–0.94)**	0.82 (0.67, 1.02)
2 Years	0.88 (0.75–1.03)	1.03 (0.87–1.20)	0.97 (0.85–1.11)	0.97 (0.85–1.10)	0.87 (0.75–1.02)	1.00 (0.82, 1.23)
White Children Only						
Prenatal	0.79 (0.57–1.09)	0.86 (0.66–1.12)	1.02 (0.83–1.25)	1.12 (0.91–1.39)	0.75 (0.54–1.04)	0.98 (0.78, 1.25)
Cord	0.64 (0.37–1.09)	**0.50 (0.32–0.80)**	1.20 (0.84–1.70)	1.38 (0.93–2.02)	**0.50 (0.28–0.92)**	0.82 (0.53, 1.25)
2 Years	0.94 (0.63–1.40)	1.16 (0.82–1.64)	1.27 (0.96–1.68)	1.14 (0.86–1.50)	1.21 (0.87–1.69)	1.42 (0.77, 2.62)
Black Children Only						
Prenatal	0.96 (0.82–1.12)	1.12 (0.96–1.31)	1.11 (0.97–1.28)	1.07 (0.93–1.22)	1.05 (0.90–1.21)	0.91 (0.77, 1.06)
Cord	1.08 (0.87–1.35)	0.88 (0.68–1.14)	0.82 (0.66–1.01)	0.86 (0.70–1.07)	0.85 (0.65–1.11)	0.81 (0.61, 1.08)
2 Years	0.91 (0.76–1.08)	1.02 (0.85–1.23)	0.91 (0.78–1.07)	0.95 (0.81–1.11)	**0.79 (0.66–0.96)**	1.02 (0.81, 1.29)

Table 5

Subgroup associations for statistically significant ($p<0.05$) interactions between prenatal 25(OH)D and other factors for each outcome. Odds ratios (95% CI) is for a 5 ng/ml increase in 25(OH)D

PRENATAL 25(OH)D		**Interaction p value**
	≥1 sIgE ≥ 0.35 IU/ml	
Mom atopic		0.04
- Yes	0.89 (0.78, 1.02)	
- No	1.10 (0.95, 1.27)	
	Doctor diagnosis of asthma 3–6 years	
C-section		
- Yes	1.16 (0.91, 1.48)	0.03
- No	0.86 (0.75, 0.98)	
Maternal education		
	Eczema	0.02
- Less than high school diploma	0.76 (0.64, 0.90)	
- At least high school diploma	1.06 (0.86, 1.30)	
Household income	≥ 1 aeroallergen sIgE ≥ 0.35 IU/ml	
≥$40,000	0.77 (0.60, 0.97)	0.04
< $40,000	1.03 (0.88, 1.20)	